REMARKS

Claims 4, 7, 10-11, 14, 17-22, 26-28, 31, 41, and 43-64 are pending in this application. Applicants thank the Examiner for withdrawing the provisional obviousness-type double patenting rejection. This reply is being filed along with a Request for Continued Examination and a Supplemental Information Disclosure Statement.

I. The Claims Are Enabled

A. Methods of Lowering Free Fatty Acids and Lowering Triglycerides

Claims 28, 31, and 43-64 are rejected under 35 U.S.C. § 112, ¶ 1, as allegedly failing to satisfy the enablement requirement. In their last response, Applicants clearly showed that there is a strong correlation between agonism at the RUP25 receptor (also known as GPR109A) and the ability of niacin to lower free fatty acids and triglycerides. In particular, Applicants submitted evidence to show that: (1) niacin was known at the time of filing to have activity in lowering triglycerides and free fatty acids; (2) the murine variant of the known RUP25 receptor was shown to mediate the metabolic effects of nicotinic acid; (3) nicotinic acid was known to bind to and agonize the RUP25 receptor; and (4) the particular species of Formula (I) recited by the claimed methods also bind to and agonize the RUP25 receptor.

In maintaining the rejection, Office first concentrates on the structural differences between niacin and the compounds of claim 4:

> Niacin is pyridine-3-carboxylic acid. The instant claims are drawn to (1H-tetrazol-5-yl)-cyclopentapyrazole compounds. Pyridine-3-carboxylic acid and (1H-tetrazol-5-yl)-cyclopentapyrazole are vastly different compounds and therefore the utility of one compound cannot be linked to the utility of the other compound.

(Final Rejection, page 3). The Office appears to have missed the significance of the evidence presented in Applicants' previous reply. The "link" between niacin and the claimed compounds is their shared ability to agonize the RUP25 receptor, not some alleged structural similarity. The RUP25 receptor has been clearly shown to be responsible for the well-documented ability of niacin to lower free fatty acids and triglycerides (see Tunaru, et al., "PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect", *Nature Medicine*, 9(3):352-355, at 354 (March 2003); and Guyton, "Effect of Niacin on Atherosclerotic Cardiovascular Disease",

Am. J. Cardiol. 82(12A):18U-23U, at page 18U (1998)). Hence, because the claimed compounds also agonize the RUP25 receptor, one of skill in the art would not have to engage in undue experimentation to practice the claimed methods.

The Office further alleges the claims are not enabled because the specification does not demonstrate that the claimed compounds can agonize the RUP25 receptor in a "predictable and consistent" manner. In particular, the Office alleges:

> Even if the two compounds were linked, the instant disclosure lacks data as to how the binding data of the instantly claimed compounds compare to the binding data of niacin. The specification at page 57 states that certain compounds of the invention have an EC50 in the nicotinic binding competition assay, but which compounds and how many?

(Final Rejection, page 3). Claim 4 recites eleven individual compound species, which have EC_{50} values in the range of about 10 to about 100 μM (see specification at page 57). Hence, it is clear which and how many compounds are active in the nicotinic binding competition assay.

Further, Applicants note that the Office has improperly framed the issue "whether the instantly claimed compounds can lower free fatty acids with a reasonable degree of certainty". The standard for enablement is not a degree of certainty, but whether one of skill in the art can practice the claimed methods without undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The predictability of the art is merely one factor in the overall analysis, which also includes 1) the quantity of experimentation necessary; 2) the amount of direction or guidance presented; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; and 7) the breadth of the claims. *Id.* Beyond the substantial teachings of the art and the large amount of guidance provided by specification regarding the correlation between agonism at the RUP25 receptor and reduction in levels of free fatty acids and triglycerides, Applicants note that a large quantity of experimentation would not be needed due to the scope of the pending claims. In particular, the currently pending claims encompass only two methods – lowering free fatty acids and triglycerides – and only eleven individual species[1]. Hence, when all of the *Wands* factors are

[1] and their pharmaceutically acceptable salt, solvates, and hydrates.

properly considered, Applicants respectfully assert that undue experimentation would not required to practice the claimed methods.

By contrast, the Office has provided no substantive evidence to counter Applicants' evidence of enablement and the assertions of the specification. As the court in *In re Marzocchi* stated, it is "incumbent upon the Patent Office...to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement". 169 U.S.P.Q. at 370 (emphasis added). The Office has provided no acceptable evidence for its allegation that a person of skill in the art could not practice the claimed methods without undue experimentation, particularly in light of the substantial evidence of enablement provided by Applicants. Applicants, therefore, respectfully assert that all of the requirements of 35 U.S.C. § 112, ¶ 1, have been met and request that the claim rejection be withdrawn.

B. Solvates and Hydrates

Claims 4, 7, 10, 11, 14, 17-22, 26-28, 31, and 41 are rejected under 35 U.S.C. § 112, ¶ 1, for allegedly failing to comply with the enablement requirement with regard to the solvates and hydrates of the claimed compounds. In particular, the Office states the following:

> Applicants arguments have been considered, but are not found persuasive. Applicants argue that solvates and hydrates are simply means to add water. Examiner respectfully disagrees that a solvate or hydrate is a compound with water. As stated previously, the term solvates and hydrates when read in the broadest reasonable sense can encompass a class of compounds that have different activity than regular compounds.

(Final Rejection, page 4).

First, a hydrate is a compound having water molecules in its crystal structure and is, to some extent, a "compound with water". Further, a hydrate clearly may be formed by exposing a non-hydrated compound to water. If the Office has some disagreement with this, Applicants request that the Office produce some evidence to the contrary.

Second, the Office appears to misconstrue Applicants' prior remarks. Applicants were not alleging that solvates and hydrates are "simply means to add water". In their prior response, Applicants contrasted the enabled multi-step methods of forming a monoclonal antibody in

Wands with the one-step process of forming a hydrate which the Office alleges is non-enabled (see Table I, reproduced below). This one-step method involves simply exposing the compound to water to determine if the compound will form a hydrate. As the production of a monoclonal antibody, as in *Wands*, is much more complex and time-consuming than the production of a hydrate or solvate, it is clearly inconsistent to allege that the production of hydrates and solvates would require undue experimentation, while the production of monoclonal antibodies in *Wands* would not require undue experimentation. A considerable amount of experimentation is permissible if it is merely routine, as in the methods of screening for hydrates and solvates. *Wands*, 8 U.S.P.Q.2d at 1404.

The Office further contends that solvates and hydrates are "a class of compounds that have different activity than regular compounds" (Final Rejection, page 4). The Office, however, has not produced any evidence that the solvates and hydrates of the claimed compounds would be expected to have radically different activity than the "regular compounds" in contravention of *In re Marzocchi*.

Indeed, *In re Marzocchi* clearly places the burden is on the Office to show that the solvates and hydrates could not be made or used without undue experimentation. Factors for consideration in determining whether undue experimentation is necessary to make and use the invention include 1) the quantity of experimentation necessary; 2) the amount of direction or guidance presented; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims.

Both the state of the art and the breadth of the claims supports the enablement of the claimed solvates and hydrates. The evidence made of record in Applicants' prior response clearly indicates that there are well-established methods of screening and characterizing hydrates and solvates.[2] Further, the art suggests that hydrates and solvates form quite readily for many

[2] See e.g., Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids", in Polymorphism in Pharmaceutical Solids, ed. Harry G. Brittain, vol. 95, chapter 5, Marcel Dekker, Inc., New York 1999, pages 183-226 (hereinafter "Guillory") at pages 202-205 and pages 205-208, describing the routine preparation of hydrates and solvates of compounds.

pharmaceutically active compounds.[3] Accordingly, there is a ample amount of direction and guidance provided by the art. Further, the claimed solvates and hydrates are limited to the solvates and hydrates of eleven individual species and their pharmaceutically acceptable salts. As stated above, a considerable amount of experimentation is permissible if it is merely routine. *Wands*, 8 U.S.P.Q.2d at 1404. In this case, only a limited number of compounds need be screened in the routine methods for producing hydrates and solvates summarized in Guillory. This clearly cannot be undue experimentation, particularly given the large amount of experimentation found permissible in *Wands*.

When all of the evidence is considered, the claimed solvates and hydrates are enabled. As the court in *In re Marzocchi* stated, it is "incumbent upon the Patent Office...to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement". 169 U.S.P.Q. at 370 (emphasis added). The Office has provided no acceptable evidence for its allegation that a person of skill in the art could not make and use the solvates and hydrates of the claimed compounds without undue experimentation. Applicants, therefore, respectfully assert that all of the requirements of 35 U.S.C. § 112, ¶ 1, have been met and request that the claim rejection be withdrawn.

Table 1

Step	Monoclonal Antibody	Hydrate or Solvate
1	immunize animal	expose the compound to water or solvent
2	remove the spleen from the immunized animal	
3	separate the lymphocytes from the other spleen cells	
4	mix the lymphocytes with myeloma cells	

[3] For example, at least one reference states that "[m]ost organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms" and that "approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates". See e.g., Vippagunta, "Crystalline Solids", Advanced Drug Delivery Reviews, 48: pages 4 and 15 (2001) (emphasis added).

Step	Monoclonal Antibody	Hydrate or Solvate
5	treat the mixture to cause fusion between the lymphocytes and the myeloma cells to make hybridomas that hopefully secrete the desired antibody	
6	separate the hybridoma cells from the unfused lymphocytes and myeloma cells by culturing in a medium in which only hybridoma cells survive	
7	culture single hybridoma cells (often 100 of different cells) in separate chambers	
8	assay the antibody secreted from each hybridoma culture to determine if it binds to the antigen	

III. The Claims Are Definite

Claim 41 is rejected under 35 U.S.C. § 112, ¶ 2, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. At page 4 of the Final Rejection, the Office alleges that:

> The amendment to the claim would be convincing if it were directed to a pharmaceutical composition, but this claim is directed to a method of producing. There are no steps to this method and therefore the claim is still indefinite.

Applicants respectfully disagree. Claim 41 recites:

> A method of producing a pharmaceutical composition comprising admixing a compound according to claim 4, or a pharmaceutically acceptable salt, solvate or hydrate thereof, with a pharmaceutically acceptable carrier.

(emphasis added). "Admixing" is clearly a step and, therefore, is not "insolubly ambiguous without a discernible meaning after all reasonable attempts at construction." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1366, 71 USPQ2d 1081, 1089 (Fed. Cir. 2004). Applicants assert that all of the requirements of 35 U.S.C. § 112, ¶ 2, have been met and request that the claim rejection be withdrawn.

III. Conclusion

Applicants respectfully assert that rejections of record have been overcome by way of this response. Allowance of all claims is respectfully requested. The Examiner is urged to contact Applicant's undersigned representative at (302) 778-8411 if there are any questions regarding the claimed invention.

The Commissioner is hereby authorized to debit any fee due or credit any overpayment to Deposit Account No. 06-1050. Further, if not accompanied by an independent petition, this paper constitutes a Petition for an Extension of Time for an amount of time sufficient to extend the deadline if necessary and authorizes the Commissioner to debit the petition fee and any other fees or credit any overpayment to Deposit Account No. 06-1050 referencing attorney docket no. 22578-0005US1.

Respectfully submitted,

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